

Contents lists available at [ScienceDirect](http://ScienceDirect.com)

# Contemporary Clinical Trials Communications

journal homepage: [www.elsevier.com/locate/conctc](http://www.elsevier.com/locate/conctc)

## Idiopathic pulmonary fibrosis: Physicians' perceptions of patient treatment with recently approved drugs



Céline Audibert\*, Christine Livoti, Alexis Caze

Deerfield Institute, 780 Third Avenue, 36th Floor, New York, NY 10017, USA

### ARTICLE INFO

#### Article history:

Received 23 February 2016

Received in revised form

5 April 2016

Accepted 24 April 2016

Available online 26 April 2016

#### Keywords:

Idiopathic pulmonary fibrosis (IPF)

Pirfenidone

Nintedanib

IPF disease severity

### ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is a rare, chronic and ultimately fatal disease for which only palliative treatments existed until recently. Between 2011 and 2015, two new drugs, pirfenidone and nintedanib, were approved in the US and Europe for the treatment of IPF, providing hope for patients. The objectives of our work were to understand physicians' expected use of these new treatments in the US and Europe, and to estimate their potential. To achieve this goal, we conducted surveys amongst US and European Union (EU) pulmonologists caring for patients with IPF. There was a significant difference between EU and US physicians in the treatment of patients with mild disease with pirfenidone; the EU physicians anticipated using pirfenidone for 57% of their patients with mild disease, whereas the US pulmonologists anticipated using it for 34% of their patients ( $p = 0.01$ ). Regarding patients with severe disease, the US pulmonologists anticipated treating 74% with either pirfenidone (46%) or nintedanib (28%), whereas the EU pulmonologists treated 28% with pirfenidone and anticipated treating 20% with nintedanib. These findings suggest treatment with pirfenidone and nintedanib based on disease severity may vary between US and EU physicians, which may affect patient outcomes.

© 2016 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## 1. Background

Interstitial lung diseases (ILD) represent a group of more than 150 disease entities, many of which are considered rare and affect fewer than 200,000 people. The etiologies, disease progression, and pathology of many rare ILDs have not yet been fully elucidated; therefore, much about this group of diseases remains unknown [1]. Among the most common ILDs is idiopathic pulmonary fibrosis (IPF), a chronic, progressive, irreversible and life-threatening ILD, the mechanism of which is unknown [2]. IPF occurs in both middle-aged and elderly adults between 40 and 70 years of age, with a mean age of 66 years at the time of diagnosis [3]; the progression of IPF from asymptomatic to symptomatic disease may occur over years or decades [4]. The disease course of IPF is variable, with both the rate of lung function decline and the eventual progression to death taking one of several clinical forms, as follows: "slow physiologic deterioration with worsening dyspnea, rapid deterioration and progression to death, or periods of relative stability interposed with periods of acute respiratory decline sometimes manifested by

hospitalization for respiratory failure" [5]. From the time of diagnosis, the median survival time among patients with IPF is two to three years, with respiratory failure secondary to disease progression representing the most common cause of death [6]. The disease's mortality rate increases with increasing age and is higher among men than women because of the associated higher rate of smoking among men. The death rate is highest during the winter, even when death resulting from infection is excluded [7]. Among previously published studies involving patients who suffered IPF-related deaths, the majority of patients experienced subacute deterioration characterized by gradually worsening symptoms over periods ranging from four weeks to several months. Additionally, a substantial proportion of patients experienced acute deterioration characterized by sudden disease progression over a four week period [8,9].

### 1.1. IPF treatment landscape

In 2011, the American Thoracic Society (ATS), the European Respiratory Society (ERS), the Japanese Respiratory Society (JRS), and the Latin American Thoracic Association (ALAT) jointly published the most recent international evidence-based guidelines regarding the diagnosis and management of IPF at the time of our

\* Corresponding author.

E-mail address: [caudibert@deerfield.com](mailto:caudibert@deerfield.com) (C. Audibert).

research [10]. Since then, the ATS, ERS, JRS and ALAT published an update of these guidelines in July 2015 due to the availability of new, important evidence for the treatment of IPF [11]. The 2011 IPF diagnosis and management guidelines noted that “the preponderance of evidence to date suggests that pharmacologic therapy for IPF is without definitive, proven benefit.” Consequently, IPF is generally considered to be unresponsive to “standard” therapies [10]. However, the recent FDA approval of two drugs, pirfenidone and nintedanib, is believed to represent a watershed event in the medical management of IPF [12]. Initial pirfenidone Phase III trial results were published in both 2010 and 2011 [13,14], and additional publications of Phase III trials involving both pirfenidone [15] and nintedanib [16] were released in 2014.

Pirfenidone's ASCEND trial was the fourth in a series of Phase III trials. The results of the previous three trials were mixed, which ultimately resulted in the approval of the drug in both Japan (October 2008) and Europe (February 2011), but not in the US. The drug's mechanism of action is unclear, although its anti-fibrotic mechanism is likely mediated via the inhibition of the expression of  $\beta 1$ , a transforming growth factor [12]. The ASCEND trial yielded positive results, as pirfenidone facilitated a significant reduction in the one year rate of decline of forced vital capacity (FVC) and a reduction in the decline in the distance achieved on the 6 min walk test; however, no effect on respiratory symptoms was noted. The results of the ASCEND trial finally garnered FDA approval for pirfenidone on October 15, 2014 [17].

The INPULSIS-1 and INPULSIS-2 trials were two randomized, double-blind, placebo-controlled trials designed to evaluate nintedanib. Nintedanib is an intracellular inhibitor that targets multiple tyrosine kinases, including vascular endothelial growth factor, fibroblast growth factor, and platelet-derived growth factor receptors, which are believed to mediate the drug's anti-fibrotic effects [12,16]. The patients who received nintedanib experienced significant reductions in their rates of FVC decline at one year, which was the primary endpoint of the two studies. Yet, the magnitude of the effect of nintedanib in terms of preventing acute exacerbations varied between the two INPULSIS trials, and there was no evidence of improvement in respiratory symptom scores. Nintedanib received FDA approval on October 15, 2014 [18].

The objectives of this study were to characterize the IPF patient population per level of severity; and to understand the potential impact of the aforementioned newly approved drugs in the treatment of patients with IPF of varying disease severity. To the best of our knowledge, this was the first research studying physicians' expected use per disease severity (mild, moderate and severe disease) of these newly approved drugs.

## 2. Methods

### 2.1. Study participants and design

Pulmonologists from the US and Europe (France, Germany, and Italy) were invited to participate in an online survey aimed at understanding current management of IPF patients, and estimating the proportion of patients that would receive pirfenidone and/or nintedanib. In the US, the known universe of 7800 pulmonologists from the CMS National Plan and Provider Enumeration System (NPPES) was established as the sample frame from which all survey recruitment was based. Given that IPF is not a commonly seen condition across all pulmonology practices, it was assumed that some screening of the general pulmonology universe would be necessary to identify physicians who see a minimum number of patients with this condition to answer the research questions in this study. To that end, we employed a two-phased approach to identify IPF treating pulmonologists. The first phase involved

sending mailed and email-based invitations to all 7800 pulmonologists in the US inviting them to participate in an online survey about the management of IPF. At this point, physicians voluntarily self-screened based on knowledge, interest, and experience level in treating this condition and had the opportunity to respond to the survey invitation by logging in to an online survey. 173 physicians responded during this first phase of recruitment and targeting. As it is unknown how many physicians successfully received, reviewed, and self-screened for this survey invitation, a true response rate cannot be calculated for this recruitment methodology. However, it is assumed that participation in this survey was random and represented basic interest and knowledge in this disease area. Out of the 173 physicians who responded to the survey invitation, 132 successfully met the minimum IPF patient requirement of 5 patients currently under management, thus representing phase 2 of the survey recruitment and targeting. These 132 physicians went on to complete the online survey and represent the study sample of IPF treating pulmonologists in the US.

In Europe, a sample frame of 1400 pulmonologists was established by assembling physicians from public sources that list IPF treating physicians and general pulmonologists such as orpha.net, Centre de Référence des Maladies Pulmonaires Rares for France, Lungenatlas for Germany and Osservatorio Malattie Rare for Italy. Similar to the US, it was also assumed that not all pulmonologists contained in the EU sample frame treat a minimum number of IPF patients so an analogous targeting and screening effort was implemented to recruit IPF treating physicians into the EU-specific survey. This effort involved sending mailed and email-based invitations to all 1400 pulmonologists contained in the sample frame inviting them to complete an online survey on the management of IPF. 82 responded to this invitation by completing the online screening questions designed to target physicians who see a minimum of 3 IPF patients. 55 physicians successfully qualified and completed the EU-based online survey. As was the case in the US, we assume that participation in the EU survey was random, voluntary, and represented basic interest and knowledge of IPF.

Both the US and EU surveys were conducted online between May and June of 2014. Physicians were offered an industry-standard honoraria amount for their time in completing the questionnaire.

### 2.2. IPF management survey

A survey was developed to assess current and expected future management of IPF patients. The online questionnaire used in the study included both quantitative and qualitative questions. Quantitative questions covered the following topics: proportion of patients per disease severity level, diagnosis location, diagnosis methods, number of new patients diagnosed per year, current prescription pattern of pirfenidone per disease severity level (EU only), awareness of data presented at a recent major medical conference, and likelihood to prescribe pirfenidone and nintedanib per disease severity level. Qualitative questions covered description of current treatment strategy, as well as knowledge of pirfenidone and nintedanib. As pirfenidone and nintedanib were not yet approved in the US, US pulmonologists were required to describe their anticipated prescription patterns for IPF before and after reviewing data from the *New England Journal of Medicine* (NEJM) publications on the ASCEND (pirfenidone) and INPULSIS (nintedanib) trials that were presented during the 2014 ATS conference in San Diego [15,16]. In the EU, as pirfenidone was already approved at the time of the survey, actual reported prescription pattern was collected. Once actual pirfenidone prescription data were collected, EU pulmonologists were also required to review the same NEJM publications as the US pulmonologists. After reviewing these data,

the responding physicians were asked how their prescription patterns for their patients would change, if at all. Both articles were made available for the physicians to consult at any time while answering the survey. The physicians were asked to estimate their prescription pattern according to patient severity levels: mild, moderate, and severe. These disease stage levels were not further described in our survey questionnaire because these have been well-defined in guidelines [10] and were supported as recognized disease stages in the interviews with experts in the field that we conducted when designing this instrument.

### 2.3. Data analysis

All survey data were analyzed in aggregate and the individual identities of the survey respondents were blinded to the study authors. The planned analyses for quantitative data were descriptive and included means and percentages.

Qualitative data were analyzed thematically and coded according to the main themes of the survey questions. Any response that addressed multiple themes was counted as multiple comments. Answers were coded in local language by native speakers. A code book was designed in order to group common theme, as well as keep any local specificity. Codes were reviewed independently by two analysts, and any discrepancies in coding were discussed until a consensus was found.

### 2.4. Ethics, consent and permissions

Data for this work were obtained through market research, and no experiment on humans has been carried out. As such, there was no institutional review board and/or licensing committee involved in approving the research, and no need for informed consent from the participants, as stated in the relevant US regulations [19]. This survey was done in accordance with market research guidelines such as the ones edited by CASRO and EPHMRA.

### 2.5. Statistical analysis

To compare the US and EU physicians' prescription rates of nintedanib and pirfenidone for patients with IPF of varying severity, Z-tests for proportions based on two independent cluster samples were conducted. The differences between the prescription rates of the US and EU physicians were considered statistically significant if the p-value for the corresponding Z-test was less than 0.05. There were no adjustments for multiple comparisons.

### 2.6. Limitations

It should be noted that this survey has a number of limitations. The questionnaire included realistic but hypothetical prescribing scenarios, and it is not possible to ascertain whether physicians would actually follow through with their stated intentions. As with any survey, our findings may be influenced by both recall and response bias of the surveyed individuals. Additionally, only a subset of pulmonologists participated in our survey, and as with all analyses, caution should be used when generalizing results to the entire population. However, the response rate obtained in our survey is in line with what could be expected for this type of survey, especially for a rare disease such as IPF [20]. In the EU, data from France, Germany and Italy were analyzed at the aggregate level. Although we realize the healthcare systems from these countries vary, those countries share the same treatment guidelines [10,11] and thus patients should receive similar treatments in all three EU countries.

## 3. Results

### 3.1. Physicians' practice

In the US, survey participants personally managed 36.1 IPF patients on average, while EU respondents managed a slightly lower average of 30.5 IPF patients. Regarding the diagnosis of IPF, the 132 US pulmonologist respondents noted that 82% of their patients were diagnosed via an HRCT scan, whereas 24% were diagnosed via biopsy. The primary reasons for performing a biopsy highlight the potential difficulties of establishing an IPF diagnosis: 59% of the respondents indicated that they performed a biopsy to confirm the diagnosis and rule out other diseases, whereas 38% indicated that the CT scan was either atypical or difficult to interpret.

The 132 US pulmonologists indicated the current management of patients with IPF depends on their symptoms, disease severity, and rate of disease progression. Primary treatment strategies – whether alone or in combination with other strategies – are described in Table 1 and involved symptom management and supportive care (58%), oxygen therapy (39%), and other specific treatments, such as steroids (37%), rehabilitation therapy or exercise (27%), and immunosuppressive agents (26%).

The EU and US survey respondents indicated the patients they treated were evenly distributed across the spectrum of disease severity, as Fig. 1 shows.

### 3.2. Pirfenidone use according to disease severity

The 2011 approval of pirfenidone in Europe provided an opportunity to compare current pirfenidone treatment trends in Europe with anticipated treatment trends in the US. In the EU, 30% of patients were currently receiving pirfenidone. When looking at the proportion per disease severity, the distribution was skewed primarily toward patients with moderate disease (51%) compared with patients with either mild (27%) or severe (22%) disease (Fig. 2).

In the US, because pirfenidone was not yet approved at the time of the survey, respondents were presented with ASCEND trial results, and were asked to provide their opinion on these trial data. US respondents were optimistic about these results, with 75% indicating they were likely to prescribe pirfenidone within six months of its approval; 23% indicated they were somewhat likely to prescribe the drug, and 2% indicated they were not likely to do so. Regarding use according to disease severity level, US physicians indicated they would most likely use pirfenidone in 44% of moderate patients, compared with 24% of patients with mild disease and 32% with severe disease (Fig. 2).

### 3.3. Expected use of nintedanib and pirfenidone

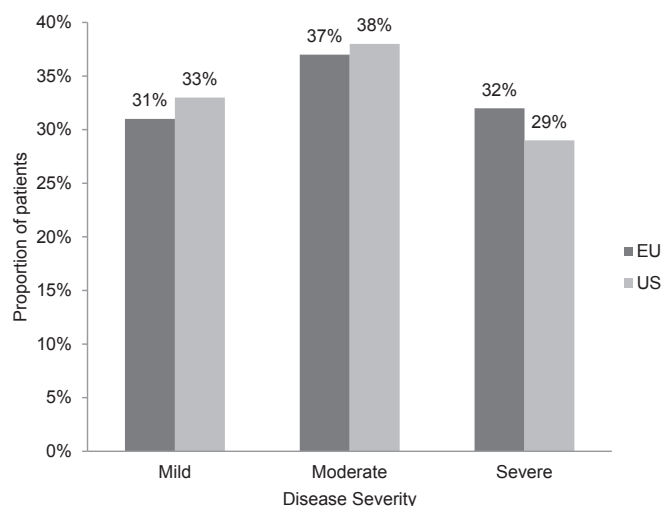
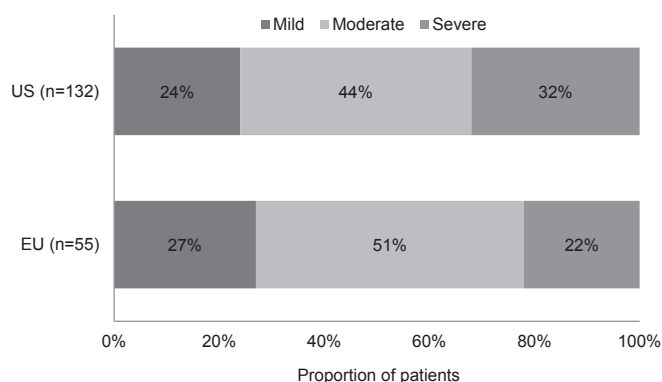
When comparing the expected usages of pirfenidone and nintedanib, the EU pulmonologists expected to prescribe pirfenidone more often than nintedanib. Although this was also true for the US physicians, their overall preference for pirfenidone was not as strong as that observed among the European physicians. Fig. 3 depicts the proportions of patients who were most likely to be treated with either drug based on disease severity and the responses of both the US and the EU survey respondents.

Regarding pirfenidone, the EU pulmonologists expected to prescribe pirfenidone to 57% of their patients with mild disease, whereas the US pulmonologists expected to prescribe pirfenidone to 34% of their mild patients ( $p = 0.01$ ). A similar trend was also anticipated for patients with moderate disease, although this trend was not statistically significant; 58% of patients with moderate disease were expected to receive pirfenidone in Europe, compared with 48% of patients with moderate disease in the US. For the

**Table 1**

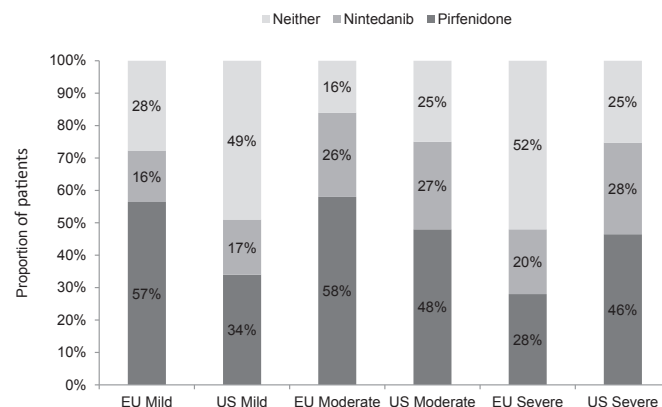
US physician-reported treatment strategies for patients with IPF (%), 2014 (N = 132).

Treatment strategy	Percent of respondents <sup>a</sup>
Treatment of symptoms in general/supportive care	58%
Oxygen therapy	39%
Steroids	37%
Rehabilitation therapy/Exercise	27%
Immuno suppressive agents (Imuran/azathioprine, cyclophosphamide)	26%
Refer patient for treatment/clinical trial	25%
N-acetylcysteine or other mucolytic agent	18%
Transplant	17%
No treatment/Observation/Watch and wait	15%
Waiting for new products (pirfenidone clearance by FDA)	12%
Treatment of gastroesophageal reflux disease	8%
Vaccination	4%
Other	8%

<sup>a</sup> The sum is greater than 100, as the respondents selected all treatment strategies that they used for their patients.**Fig. 1.** Disease severity per region.**Fig. 2.** Pirfenidone prescription per disease severity.

patients with severe disease, the opposite trend was observed, as 46% of severe patients were expected to receive pirfenidone in the US, compared with 28% of the severe patients in Europe.

Regarding nintedanib, the EU and US pulmonologists anticipated treating similar proportions of patients with mild disease (16% and 17%, respectively) and moderate disease (26% and 27%, respectively). The US respondents expected to use nintedanib to treat 28% of their patients with severe disease, while the EU

**Fig. 3.** Anticipated pirfenidone and nintedanib usage per region per disease severity.

respondents anticipated using it to treat 20% of their patients with severe disease.

#### 4. Discussion

The absence of adequate treatment options for IPF management has long plagued physicians. In 2014, the expected availability of two new drugs with different hypothesized mechanisms of action, encouraging efficacy data, and manageable side effect profiles suggested that the treatment armamentarium of pulmonologists may be strengthened significantly via the drugs' emergence. With changes in the therapeutic landscape came the need to evaluate the potential impact of these two new drugs, nintedanib and pirfenidone, on IPF management.

During our survey, participating pulmonologists were presented with NEJM publications pertaining to the ASCEND (pirfenidone) and INPULSIS (nintedanib) [15,16] trials, as these were the most current and reliable sources of information pertaining to the two drugs. As Hunninghake mentioned in his NEJM editorial, the field should be cautious about extrapolating the findings of the INPULSIS and ASCEND trials to patients outside the recruitment criteria for these trials, as "the studies provide little insight into the use of these drugs in patients with more severe disease (FVC <50% of the predicted value) or with an acute disease exacerbation" [12]. Although there were no data supporting the use of either pirfenidone or nintedanib for patients with severe disease, we nonetheless included this patient population in our assessment, as it represents a significant proportion of the patients with IPF.

These results identified a statistically significant difference



between the EU and US pulmonologists in the use of pirfenidone to treat patients with mild disease. EU respondents anticipated prescribing pirfenidone for 57% of their patients with mild disease, whereas the US pulmonologists anticipated prescribing it for only 34% of those patients ( $p = 0.01$ ). Additionally, for the patients with severe disease, the US pulmonologists anticipated treating a total of 74% of these patients with either pirfenidone (46%) or nintedanib (28%), whereas the EU pulmonologists anticipated treating a total of 48% of their patients with either pirfenidone (28%) or nintedanib (20%). These differences may exist for several reasons. First, pirfenidone was not indicated for patients with severe disease in Europe at the time of the survey (pirfenidone was still not indicated for severe patients at the time of this article's submission). Consequently, the EU pulmonologists may have been less likely to treat patients with severe disease with pirfenidone and less likely to anticipate treating a large proportion of said patients with nintedanib. Second, because pirfenidone was approved by the EMA in 2011, the EU pulmonologists had the opportunity for first-hand experience in using the drug and may have observed better outcomes among patients with either mild or moderate IPF. Third, the observation that US physicians anticipated treating a higher proportion of patients with severe IPF may reflect a more aggressive approach by US physicians to the treatment of severely ill patients compared with EU physicians. Fourth, the likelihood of off-label use to treat patients with severe IPF may differ between US and EU physicians.

The results of our survey also indicate pirfenidone appears to be the preferred agent across the entire spectrum of disease severity. This may be because pirfenidone was already being used in Europe at the time of the survey, and EU doctors may have been less willing to transition their patients to nintedanib. In the US, the observed preference for pirfenidone may be attributed to the increased awareness of pirfenidone because of its development history. Pirfenidone's New Drug Application (NDA) was first submitted to the FDA in November 2009, whereas nintedanib's NDA was submitted to the FDA in May 2014.

Another critical dimension of the management of IPF is the establishment of disease severity after diagnosis. The complex nature of IPF in combination with the variability of the disease's course complicates both its diagnosis and its treatment. The ATS, ERS, JRS, and ALAT clinical practice guidelines published in 2011 recommend the use of a multidisciplinary approach to diagnose IPF; however, the use of a multidisciplinary approach is not always feasible, and there likely exists some degree of variability in both the diagnosis and the treatment of patients with IPF in clinical practice [10]. Despite these guidelines, the division of IPF cases based on disease severity remains both challenging and somewhat subjective. In our survey, 59% of the US respondents indicated that they performed a biopsy to confirm the diagnosis and rule out other diseases, whereas 38% indicated that CT scans were either atypical or difficult to interpret. These findings emphasize the challenges of establishing a diagnosis and determining the disease's severity.

Because both pirfenidone and nintedanib are now approved in Europe and the US, patients and physicians have treatment options for a rare disease for which there were previously no approved treatments. Accordingly, the 2011 ATS, ERS, JRS, and ALAT clinical practice guidelines were updated in 2015 to provide recommendations on pirfenidone and nintedanib use, amongst other treatment [11]. The revised guidelines provide a positive recommendation on the use of these two new drugs. However, the use of these drugs and their impact on diagnosis and disease severity remain to be seen, underscoring the need for additional research studies to improve both the understanding and the

management of IPF.

## 5. Conclusion

In conclusion, the availability of these two agents has provided clinicians with hope for halting disease progression and has given them additional tools with which to manage this complex disease. However, the true impact of these drugs on patient diagnosis, management, and survival remains unclear until long-term, real world data becomes available.

## Acknowledgments

We thank Zheng Su, PhD for assisting with the statistical analysis and Daniel Glass, PhD for reviewing the manuscript.

## References

- [1] M. Demedts, A.U. Wells, J.M. Anto, U. Costabel, R. Hubbard, P. Cullinan, *Interstitial lung diseases: an epidemiological overview*, *Eur. Respir. J. Suppl.* 18 (2001) 2s–16s.
- [2] D.B. Coultas, R.E. Zumwalt, W.C. Black, R.E. Sobonya, The epidemiology of interstitial lung diseases, *Am. J. Respir. Crit. Care Med.* 150 (1994) 967–972, <http://dx.doi.org/10.1164/ajrccm.150.4.7921471>.
- [3] American Thoracic Society & the European Respiratory Society (ERS), Idiopathic pulmonary fibrosis: diagnosis and treatment, *Am. J. Respir. Crit. Care Med.* 161 (2000) 646–664, <http://dx.doi.org/10.1164/ajrccm.161.2.ats3-00>.
- [4] S.G. Ziegler, K. Wilson, W.A. Gahl, J. Moss, B.R. Gochoico, S. El-Chemaly, *Familial pulmonary fibrosis: natural history of preclinical disease*, *Am. J. Respir. Crit. Care Med.* 181 (2010) A2980.
- [5] B. Ley, H.R. Collard, T.E. King, Clinical course and prediction of survival in idiopathic pulmonary fibrosis, *Am. J. Respir. Crit. Care Med.* 183 (2011) 431–440, <http://dx.doi.org/10.1164/rccm.201006-0894CI>.
- [6] American Thoracic Society & European Respiratory Society, International multidisciplinary consensus classification of the idiopathic interstitial pneumonias, *Am. J. Respir. Crit. Care Med.* 165 (2002) 277–304, <http://dx.doi.org/10.1164/ajrccm.165.2.ats01>.
- [7] A.L. Olson, J.J. Swigris, G. Raghu, K.K. Brown, Seasonal variation: mortality from pulmonary fibrosis is greatest in the winter, *Chest* 136 (2009) 16–22, <http://dx.doi.org/10.1378/chest.08-0703>.
- [8] E.R.F. Pérez, C.E. Daniels, D.R. Schroeder, J.S. Sauver, T. Hartman, B.J. Bartholmai, et al., Incidence, prevalence, and clinical course of idiopathic pulmonary fibrosis: a population-based study, *Chest* 137 (2010) 129–137, <http://dx.doi.org/10.1378/chest.09-1002>.
- [9] F.J. Martinez, The clinical course of patients with idiopathic pulmonary fibrosis, *Ann. Intern. Med.* 142 (2005) 963–967, [http://dx.doi.org/10.7326/0003-4819-142-12\\_Part\\_1-200506210-00005](http://dx.doi.org/10.7326/0003-4819-142-12_Part_1-200506210-00005).
- [10] G. Raghu, H.R. Collard, J.J. Egan, F.J. Martinez, J. Behr, K.K. Brown, et al., An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management, *Am. J. Respir. Crit. Care Med.* 183 (2011) 788–824, <http://dx.doi.org/10.1164/rccm.2009-040GL>.
- [11] G. Raghu, B. Rochwerg, Y. Zhang, C.A.C. Garcia, A. Azuma, J. Behr, et al., An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management – an update of the 2011 clinical practice guideline, *Am. J. Respir. Crit. Care Med.* 192 (2015) e3–e19, <http://dx.doi.org/10.1164/rccm.201506-1063ST>.
- [12] G.M. Hunninghake, A new hope for idiopathic pulmonary fibrosis, *N. Engl. J. Med.* 370 (2014) 2142–2143, <http://dx.doi.org/10.1056/NEJMe1403448>.
- [13] H. Taniguchi, M. Ebina, Y. Kondoh, T. Ogura, A. Azuma, M. Suga, et al., Pirfenidone in idiopathic pulmonary fibrosis, *Eur. Respir. J.* 35 (2010) 821–829, <http://dx.doi.org/10.1183/09031936.00005209>.
- [14] P.W. Noble, C. Albera, W.Z. Bradford, U. Costabel, M.K. Glassberg, D. Kardatzke, et al., Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials, *Lancet* 377 (2011) 1760–1769, [http://dx.doi.org/10.1016/S0140-6736\(11\)60405-4](http://dx.doi.org/10.1016/S0140-6736(11)60405-4).
- [15] T.E. King Jr., W.Z. Bradford, S. Castro-Bernardini, E.A. Fagan, I. Glaspole, M.K. Glassberg, et al., A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis, *N. Engl. J. Med.* 370 (2014) 2083–2092, <http://dx.doi.org/10.1056/NEJMoa1402582>.
- [16] L. Richeldi, R.M. du Bois, G. Raghu, A. Azuma, K.K. Brown, U. Costabel, et al., Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis, *N. Engl. J. Med.* 370 (2014) 2071–2082, <http://dx.doi.org/10.1056/NEJMoa1402584>.
- [17] U.S. Food and Drug Administration, FDA approves Esbriet to treat idiopathic pulmonary fibrosis, FDA News Release (2014). Available: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm418991.htm>, accessed 08.04.15.
- [18] U.S. Food and Drug Administration, FDA approves Ofev to treat idiopathic

- pulmonary fibrosis, FDA News Release (2014). Available: <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm418994.htm>. accessed 08.04.15.
- [19] HHS.gov US Department of Health and Human Services. <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.102>.
- [20] Pew Research Center, Assessing the Representativeness of Public Opinion Surveys, 2012. Available: <http://www.people-press.org/2012/05/15/assessing-the-representativeness-of-public-opinion-surveys/>.